REMARKS AND ARGUMENTS

All Claims have been amended, where applicable, to change "DNA sequence" to –gene–. Basis for these amendments is found, for example, in the specification at page 11, line 19 through page 12, line 13, and in Claims 46, 42, 41, and 31 as originally filed.

Claims 129 and 130 have been canceled.

Claims 1-8, 11-14, 17, 31-41, 48, 59-70, 73-76, 79, 83, 86-87, 105-114, 116, 118, 120, and 122-128, and 131-133 remain in the application.

Claims 31-41, 48, 59-70, 73-76, 79, 83, 86-87, 105-114, 116, 118, 120, 122-126, 128, and 131-133, which have been held to be withdrawn from consideration, remain pending in the application.

The Office's attention is particularly directed to Claim 17, which, through an apparent clerical error, had been omitted from the listing of pending Claims in line 4 of the August 18, 2006 "Office Action Summary," form PTOL-326.

Reexamination and reconsideration of the application, as amended, are respectfully requested.

Applicants are paying $690 in total fees by credit card, through Private PAIR, as a small entity: $510 to extend the date for response from November 18, 2006 to February 20, 2007, plus $180 for the accompanying new Information Disclosure Citation. If any additional extension of time is required, please consider this paper a petition for the total extension of time required. If the fee has been calculated or paid incorrectly, please refer to the Deposit Account Authorization previously filed with this application.

Two Grounds of Rejection Have Been Made Moot by Cancellation of Claims

Two grounds of rejection – the § 101 rejection, and the § 112, first paragraph enablement rejection – had been entered only against Claims 129 and 130. Claims 129 and 130 have been canceled. These two grounds of rejection are therefore now moot, and will not be discussed further.

The Restriction Requirement, and the Pending Petition

On September 18, 2006 the Applicants filed a "Petition to Group 1600 Technology Center Director under 37 C.F.R. § 1.144 to Review Final Restriction Requirement." As of the date the present Amendment is being transmitted to the Office, the undersigned had not received a Decision on this Petition.

For the reasons given in the Petition, the Examiner is respectfully requested to withdraw the restriction requirement in its entirety, and to examine all pending Claims on their merits.

Strictly in the alternative, and in the interest of promoting overall efficiency in prosecution, the Examiner is respectfully requested to consider whether to defer further action on the merits of the application until after the September 18, 2006 Petition has been decided.

The Examiner's assistance is respectfully requested in inquiring about the status of the pending Petition from the Technology Center Director, in case the Petition has not already been decided when this application otherwise comes up for action by the Examiner.

The Obviousness-Type Double Patenting Rejection

Several Claims were rejected for obviousness-type double patenting over the Claims of U.S. Patent 6,635,740.

The August 18, 2006 Office Action at page 3, second paragraph, acknowledged that this rejection could be overcome by a terminal disclaimer.

The Office's attention is respectfully directed to the Terminal Disclaimer that is already of record in this application, having been filed on July 11, 2003.

It is respectfully submitted that the earlier Terminal Disclaimer makes this ground of rejection moot. Strictly in the alternative, should the Office believe that there is some deficiency in the earlier Terminal Disclaimer, then the Office is respectfully requested to clarify so that a more responsive reply might be made.

Otherwise, it is respectfully submitted that this ground of rejection is moot.

The § 112, First Paragraph Rejection (New Matter)

Claims 1-8, 11-14, 17, and 127 were rejected as not complying with the written description requirement of 35 U.S.C. § 112, first paragraph. In particular, the Office has suggested that the scope of the term "DNA sequence encoding _____." differs from the scope of the term "gene encoding _____."

Without conceding that the Office's contention is correct, the Applicants have amended the Claims to make the rejection moot. All relevant Claims have been amended to recite a --gene-- rather than a "DNA sequence."

The Office has acknowledged that the specification describes "genes encoding" the recited peptides. (August 18, 2006 Office Action, pages 4-5; see also the specification at page 11, line 19 through page 12, line 13, and Claims 46, 42, 41, and 31 as originally filed.) The present amendments conform the language of the Claims to that which expressly appears in the specification, namely "gene." Thus this ground of rejection has become moot.

The § 112, First and Second Paragraph Rejections (Analogs)

Two of the grounds of rejection were conceptually similar, and will be treated together in this reply. Claims 1-8, 11-14, 17, and 127 were rejected under § 112, first paragraph as lacking written description for "analogs" of the recited hormones or lytic peptides. Claims 1, 3, and 127 were also rejected under § 112, second paragraph as being indefinite in their use of the term "analogs."

Preliminary Remarks Concerning Analogs

It should be kept in mind that the disclosure of a patent specification is directed not to the layperson, but to a person of ordinary skill in the art. That which is known to those of skill in the art need not be disclosed. It is well-settled that a patent specification need not be, and should not be, a catalogue of existing technology. A patent specification need not teach, and preferably omits, what is well known in the art.

As is well known in the art, an analog is a compound with a structure that is similar to that of the "parent" compound, and that has similar or opposing metabolic effects. Hormone analogs may act either as agonists, having a similar effect, or antagonists, having a blocking effect.

Furthermore, the present specification provides ample guidance to a worker of ordinary skill in the art (if, indeed, additional guidance is needed) as to what constitutes analogs of the recited hormones. See, e.g., the specification at page 2, lines 25-28; page 6, lines 11-15; page 7, lines 7-26; page 8, lines 7-13; page 8, lines 20-23; page 9, lines 7-14; page 12, line 28 through page 13, line 3; page 17, lines 13-14; page 18, lines 12-20; page 32, lines 17-18; page 33, lines 6-7; and page 42, lines 7-18. Note also the incorporation by reference of all cited references at page 43, lines 1-6.

Numerous hormone analogs were well-known in the art as of the March 27, 1998 international filing date of the "parent" application. Numerous lytic peptide analogs were also well-known in the art as of the international filing date. The references discussed below are representative of what was available in the literature at the time, but are not presented as an exhaustive list.

All references discussed below, except for Raynor *et al.*, were cited in the July 11, 2003 Information Disclosure Citation. The Raynor *et al.* paper is being cited in a new Information Disclosure Citation that is being contemporaneously submitted.

A note concerning the nomenclature used in the following discussion: The hormone analogs that are discussed in the literature include both: **(1)** peptide analogs that either were or potentially could be encoded in DNA, transcribed into mRNA, and translated by ribosomes in accordance with the standard genetic code (including forms that will naturally be modified *in vivo* post-translationally, e.g., by glycosylation); and **(2)** peptide or non-peptide analogs that could not be directly expressed by ribosomes, for example because they incorporate D-amino acids or other non-standard amino acids. For purposes of simplicity, the former will sometimes be called "ribosomal analogs," and the latter "non-ribosomal analogs."

Analogs of Gonadotropin Releasing Hormone

As of the March 27, 1998 international filing date of the "parent" application, there were numerous published references disclosing analogs of gonadotropin releasing hormone (GnRH), also known as luteinizing hormone releasing hormone (LHRH). Following are a few of many examples.

S. Sealfon *et al.*, "Molecular mechanisms of ligand interaction with the gonadotropin-releasing hormone receptor," *Endocrine Reviews*, vol. 18, pp. 180-205 (1997) is a review paper that, among other things, discusses the apparent role of each of the individual amino acids in the GnRH decapeptide, and gives extensive guidance on the types of substitutions that may be made in analogs. See particularly pp. 184-191 of this paper, and the schematic summary shown in Fig. 8 on page 190.

A 1986 review paper, M. Karten *et al.*, "Gonadotropin-releasing hormone analog design. Structure-function studies toward the development of agonists and antagonists: rationale and perspective," *Endocrine Reviews*, vol. 7, pp. 44-66 (1986), described or gave citations to over 2000 GnRH analogs (p. 44, par. 1) that had been synthesized and characterized over a decade before the filing date of the present application. Many specific examples were given directly in the review paper itself, examples of both ribosomal and non-ribosomal analogs.

S. Sealfon *et al.*, "The gonadotrophin-releasing hormone receptor: structural determinants and regulatory control," *Human Reproduction Update*, vol. 1, pp. 216-230 (1995) provides a review of contemporaneous knowledge of GnRH receptor structure and regulation of receptor expression. This review article mentions the fact that thousands of GnRH analogs have been synthesized and studied (p. 216). Information about the structure of the receptor has been used in the rational design of new GnRH analogs (p. 222).

A. Nechushtan *et al.*, "Adenocarcinoma cells are targeted by the new GnRH-PE_{66} chimeric toxin through specific gonadotropin-releasing hormone binding sites," *J. Biol. Chem.*, vol. 298, pp. 11597-11603 (1997) discloses a 67 kDa chimeric fusion protein comprising a *Pseudomonas*-derived toxin bound to a GnRH analog in which tryptophan replaced glycine as the sixth amino acid; as well as the use of that fusion protein to prevent

the growth of colon carcinoma xenografts in nude mice, and to kill various adenocarcinoma cells *in vitro*.

Nett *et al.*, published international patent application WO 90/09799 discloses several I-LHRH-III (GnRH-III) analogs, including both ribosomal peptide analogs and non-ribosomal peptide analogs. For example, at p. 11 is the disclosure that amino acid substitutions at the 6 position of the GnRH molecule yield analogs with high affinity for GnRH receptors, with preferred amino acid substitutions including lysine, aspartic acid, glutamic acid, and cysteine.

Analogs of Luteinizing Hormone, Chorionic Gonadotropin, and Their Beta Subunits

Luteinizing hormone and chorionic gonadotropin are structurally and functionally homologous peptides. See, e.g., J. Lin *et al.*, "Increased expression of luteinizing hormone / human chorionic gonadotropin receptor gene in human endometrial carcinomas," *J. Clinical Endocrinology & Metabolism*, vol. 79, pp. 1483-1491 (1994).

D. Morbeck *et al.*, "A receptor binding site identified in the region 81-95 of the β-subunit of human luteinizing hormone (LH) and chorionic gonadotropin (hCG)," *Molecular & Cellular Endocrinology*, vol. 97, pp. 173-181 (1993) discloses experiments in which two series of overlapping peptides (each 15 residues in length), comprising the entire sequences of the β-subunits of human lutropin (LH) and choriogonadotropin (hCG), were used to identify all linear regions of the subunit that participate in the binding of the hormone to the receptor. The most potent inhibitor in a competitive binding assay was a peptide containing residues 81-95 of hCG. In addition, other regions that inhibited binding were identified. A third set of peptides was prepared in which each residue of the 81-95 hCG sequence was sequentially replaced by alanine, to identify the more important residues for binding. Five such residues were identified as being important to binding. In addition to identifying the 81-95 hCG sequence as itself being a useful analog, this detailed information would be very useful in designing analogs of the beta subunit of luteinizing hormone or of chorionic gonadotropin.

V. Garcia-Campayo *et al.*, "Design of stable biologically active recombinant lutropin analogs," Nature Biotechnology, vol. 15, pp. 663-667 (1997) describes the synthesis of a ribosomal luteinizing hormone analog, in which the α and β subunits were fused through a linker. The analog was found to be biologically active, and to have significantly greater *in vitro* stability than the native heterodimer.

T. Sugahara *et al.*, "Biosynthesis of a biologically active single peptide chain containing the human common α and chorionic gonadotropin β subunits in tandem," *Proc. Natl. Acad. Sci. USA*, vol. 92, pp. 2041-2045 (1995) describes the production of a chimeric peptide, in which the α and β subunits of human chorionic gonadotropin were fused into a single polypeptide chain. The resulting molecule was found to be efficiently secreted, and to show increased activity both *in vitro* and *in vivo*.

D. Puett *et al.*, "The tie that binds: Design of biologically active single-chain human chorionic gonadotropins and a gonadotropin-receptor complex using protein engineering," *Biol. Repro.*, vol. 58, pp. 1337-1342 (1998) is a review of numerous published papers concerning human chorionic gonadotropin and its ribosomal and non-ribosomal analogs, including the effects of chemical modifications, synthetic peptides, limited proteolysis, protein engineering to produce hormone chimeras, site-directed mutagenesis, and specific amino acid residues.

Y. Han *et al.*, "hCGβ Residues 94-96 alter LH activity without appearing to make key receptor contacts," *Mol. Cell. Endocrin.*, vol. 124, pp. 151-161 (1996) describes the effects on LH activity of several particular amino acid substitutions in the beta subunit of LH (namely, at residues 94-96). Not only are numerous ribosomal analogs specifically described in this paper, but this type of information provides important guidance to one of skill in the art in designing other analogs.

Z. Zalesky *et al*, "Ovine luteinizing hormone: Isoforms in the pituitary during the follicular and luteal phases of the estrous cycle and during anestrus," *J. Anim. Sci.*, vol. 70, pp. 3851-3856 (1992) discloses thirteen isoforms of LH in ewes. Each of these thirteen isoforms could be considered a ribosomal analog of LH.

Follicle Stimulating Hormone

J. Dias *et al*, "Human follicle-stimulating hormone structure-activity relationships," *Biol. Repro.*, vol. 58, pp. 1331-1336 (1998) is a review of numerous publications concerning human follicle stimulating hormone, structure-activity relationships, and FSH analogs, including the effects of glycosylation, synthetic peptides, site-directed mutagenesis, and specific amino acid residues. Many of the analogs were ribosomal analogs.

A. Cerpa-Poljak, "Isoelectric charge of recombinant human follicle-stimulating hormone isoforms determines receptor affinity and *in vitro* bioactivity," *Endocrinology*, vol. 132, pp. 351-356 (1993) discloses the preparation of several isoforms of human recombinant FSH. Each of the isoforms may be considered an FSH ribosomal analog.

P. Grasso *et al.*, "*In vivo* effects of follicle-stimulating hormone-related synthetic peptides on the mouse estrous cycle," *Endocrinology*, vol. 137, pp. 5370-5375 (1996) discloses a synthetic tetrapeptide amide analog to the beta subunit of FSH, and its antagonistic effects both *in vitro* and *in vivo*.

Somatostatin

K. Raynor *et al.*, "Cloned Somatostatin Receptors: Identification of Subtype-Selective Peptides and Demonstration of High Affinity Binding of Linear Peptides," *Molec. Pharmacol.*, vol. 43, pp. 838-844 (1993) discloses a number of somatostatin peptide analogs (e.g., Table I). While these analogs are not themselves ribosomal analogs, a person of ordinary skill in the art could readily convert many, perhaps most, of them with ribosomal analogs by replacing D-amino acids with L-amino acids, by replacing a non-standard amino acid with an analogous "standard" amino acid, or both.

Lamprey III Luteinizing Hormone Releasing Hormone (l-LHRH-III, or GnRH-III)

I. Mezö *et al.*, "Synthesis of Gonadotropin-Releasing Hormone III Analogs. Structure-Antitumor Activity Relationships," *J. Med. Chem.*, vol. 40, pp. 3353-3358 (1997) discloses several l-LHRH-III (GnRH-III) analogs, including both ribosomal analogs and non-ribosomal analogs.

S. McCann *et al.*, "FSH-Releasing Peptides," published international application WO 98/55136 discloses several I-LHRH-III (GnRH-III) analogs, including both ribosomal peptide analogs and non-ribosomal peptide analogs. See pp. 12-15. (Note: The '136 PCT application was published after the international filing date of the "parent" application from which the present application claims priority, but its disclosure was incorporated into the specification of the present application and its "parent" application by reference. See, e.g., the present specification at p. 43, lines 1-6.)

Melanocyte-Stimulating Hormone

The sequence of an αMSH analog is given in the specification at page 32, lines 17-18 (SEQ ID NO. 10).

Lytic peptide analogs

Pages 5-7 of the August 18, 2006 Office Action also mentioned analogs of certain lytic peptides. The bulk of the Office's comments appeared to be directed to objections to hormone analogs, rather than to lytic peptide analogs. Nevertheless, if the Applicants have interpreted the Office Action correctly, it appears that the Office has also objected to the "analog" language in the following limitation from Claim 3: "said lytic peptide domain is selected from the group consisting of a cecropin peptide, a melittin peptide, a defensin peptide, a magainin peptide, a sarcotoxin peptide, and analogs of said peptides."

It is respectfully submitted that the behavior of analogs of known lytic peptides is relatively predictable, and that the present specification provides a more than adequate disclosure to support the claim limitations directed to analogs of certain lytic peptides.

It should be kept in mind that lytic peptides disrupt cell membranes non-specifically. It is believed that lytic peptides disrupt cell membranes by opening holes or channels in the membranes by virtue of the lytic peptides' amphipathic charge distribution. Lytic peptides do not bind to specific receptor molecules, so there is no need for specificity. There has been sufficient work done in the field of lytic peptides that it has become fairly predictable, at least in broad strokes, which lytic peptide analogs should reasonably be expected to have membrane-lysing activity.

An extensive discussion of lytic peptides appears in the specification at page 36, line 4 through page 42, line 18. Portions of that discussion are excerpted here: Lytic peptides are small, basic peptides. Native lytic peptides appear to be major components of the antimicrobial defense systems of a number of animal species, including those of insects, amphibians, and mammals. They typically comprise 23-39 amino acids, although they can be smaller. They have the potential for forming amphipathic alpha-helices. Known amino acid sequences for lytic peptides may be modified to create new peptides that would also be expected to have lytic activity by substitutions of amino acid residues that preserve the amphipathic nature of the peptides (e.g., replacing a polar residue with another polar residue, or a non-polar residue with another non-polar residue, etc.); by substitutions that preserve the charge distribution (e.g., replacing an acidic residue with another acidic residue, or a basic residue with another basic residue, etc.); or by lengthening or shortening the amino acid sequence while preserving its amphipathic character or its charge distribution. Families of naturally-occurring lytic peptides include the cecropins, the defensins, the sarcotoxins, the melittins, and the magainins. Tests with synthesized, nonhomologous analogs of different classes of lytic peptides have shown that a positively charged, amphipathic sequence containing at least 20 amino acids appears to be a requirement for lytic activity in some classes of peptides. Other work has shown that smaller peptides, having as few as 10-14 amino acid residues, can also be lytic.

The extensive guidance provided in the specification, as well as general knowledge in the field concerning lytic peptides, provides an adequate written description of the lytic peptide analogs recited in Claim 3, and that a worker of ordinary skill in the art would find the recited analogs to be reasonably definite.

Analog Summary

Analogs of the hormones and lytic peptides recited in the Claims were well known in the art as of the filing date of the present application. A patent specification need not teach, and preferably omits, what was well known in the art. A person of ordinary skill in the art would have readily understood what was meant by "analog" in this context, and

would have found that term to be reasonable definite. The § 112, first and second paragraph "analog" grounds of rejection should be withdrawn.

Further Remarks Concerning Dependent Claims 5-8, 11-14, and 17

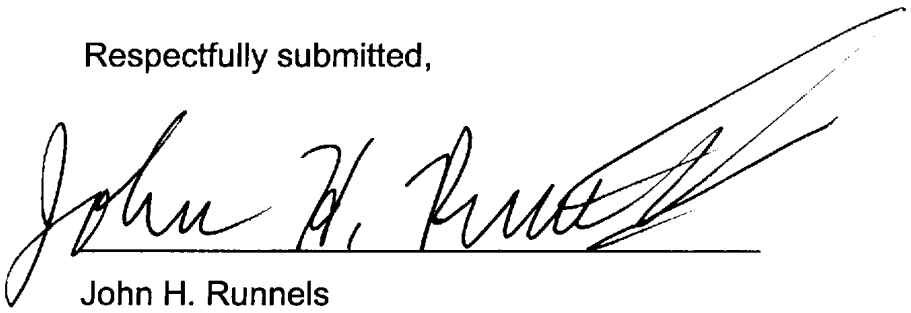
Strictly in the alternative, it is respectfully submitted that the § 112, first paragraph rejection is clearly inapplicable to dependent Claims 5-8, 11-14, and 17, due to the more specific limitations appearing in each of those Claims. For the reasons given above, it is respectfully submitted that the § 112, first paragraph rejection concerning analogs should be withdrawn for all Claims. Strictly in the alternative, it is respectfully submitted that the § 112, first paragraph rejection should be withdrawn at least for dependent Claims 5-8, 11-14, and 17, for which the rationale given in the Office's rejections would seem to be inapplicable.

Conclusion

The restriction requirement should be withdrawn, and all Claims should be examined on their merits.

Allowance of all pending Claims at an early date is respectfully requested.

Respectfully submitted,



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